

WE CLAIM:

1. A method of treating a patient with diabetes mellitus, comprising the steps of:

5 (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor; and

(b) transferring the stem cell into the patient, wherein the stem cell differentiates into an insulin-producing cell.

10 2. The method of claim 1, wherein the patient serves as the donor for said stem cells of step a.

15 3. The method of claim 1 wherein, prior to the step of transferring, the stem cell is treated *ex vivo* with an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

4. The method of claim 1, wherein the step of transferring is performed via endoscopic retrograde injection.

20 5. The method of claim 1 additionally comprising the step of:  
(c) treating the patient with an immunosuppressive agent.

6. The method of claim 5, wherein the immunosuppressive agent is selected from the group consisting of FK-506, cyclosporin, and GAD65 antibodies.

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7. A method of treating a patient with diabetes mellitus, comprising the steps of:  
(a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) expanding the stem cell *ex vivo* to produce a progenitor cell; and  
(c) transferring the progenitor cell into the patient, wherein the progenitor cell differentiates into an insulin-producing beta cell.

5     8.     The method of claim 7, wherein the patient serves as the donor for said stem cells of step a.

9.     The method of claim 7, wherein the step of expanding is performed in the presence of an agent selected from the group consisting of EGF, bFGF-2, high  
10    glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

10.    The method of claim 7, wherein the step of transferring is performed via endoscopic retrograde injection.

15     11.    The method of claim 7 additionally comprising the step of:  
(d) treating the patient with an immunosuppressive agent.

12.    The method of claim 11, wherein the immunosuppressive agent is selected  
20    from the group consisting of FK-506, cyclosporin, and GAD65 antibodies.

13.    A method of treating a patient with diabetes mellitus, comprising the steps of:  
(a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;  
25    (b) expanding the stem cell to produce a progenitor cell;  
(c) differentiating the progenitor cell in culture to form pseudo-islet like aggregates; and  
(d) transferring the pseudo-islet like aggregates into the patient.

14. The method of claim 13, wherein the patient serves as the donor for said stem cells of step a.

5 15. The method of claim 13, wherein the step of expanding is performed in the presence of an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

10 16. The method of claim 13, wherein the step of transferring is performed via endoscopic retrograde injection.

17. The method of claim 13 additionally comprising the step of:  
(e) treating the patient with an immunosuppressive agent.

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18. The method of claim 17, wherein the immunosuppressive agent is selected from the group consisting of FK-506, cyclosporin, and GAD65 antibodies.

19. A method of isolating a stem cell from a pancreatic islet of Langerhans,  
20 comprising the steps of:

- (a) removing a pancreatic islet from a donor;
- (b) culturing cells from the pancreatic islet; and
- (c) selecting a nestin-positive clone from the culture.

25 20. The method of claim 19, wherein the culturing is first performed in a vessel coated with concanavalin A and then again performed in a vessel not coated with concanavalin A.

21. The method of claim 19 comprising the additional step of:

(d) expanding the nestin-positive clone by treatment with an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, GLP-1, exendin-4, IDX-1, a nucleic acid molecule encoding IDX-1, betacellulin, activin A, TGF- $\beta$ , and combinations thereof.

22. A method of inducing the differentiation of a nestin-positive pancreatic stem cell into a pancreatic progenitor cell, comprising the step of:

treating a nestin-positive pancreatic stem cell with an agent selected from the group consisting of EGF, bFGF-2, high glucose, KGF, HGF/SF, IDX-1, a nucleic acid molecule encoding IDX-1, GLP-1, exendin-4, betacellulin, activin A, TGF- $\beta$ , and combinations thereof, whereby the stem cell subsequently differentiates into a pancreatic progenitor cell.

23. The method of claim 22, wherein the pancreatic progenitor cell subsequently forms pseudo-islet like aggregates.

24. An isolated, nestin-positive human pancreatic or liver stem cell that is not a neural stem cell.

25. The isolated stem cell of claim 24 that differentiates to form insulin-producing beta cells.

26. The isolated stem cell of claim 24 that differentiates to form glucagon-producing alpha cells.

27. The isolated stem cell of claim 24 that differentiates to form pseudo-islet like aggregates.

28. The isolated stem cell of claim 24 that differentiates to form hepatocytes.
29. The isolated stem cell of claim 24 that does not express class I MHC antigens.

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30. A method of identifying a pancreatic cell as a stem cell, comprising the step of:  
contacting a cell with a labeled nestin-specific antibody, whereby if the cell  
becomes labeled with the antibody the cell is identified as a stem cell.

- 10 31. The method of claim 30 further comprising the step of:  
contacting the cell with a labeled cytokeratin-19 specific antibody, whereby if  
the cell does not become labeled with the antibody the cell is identified as a stem  
cell.

- 15 32. The method of claim 30 or 31 further comprising the step of:  
contacting the cell with a labeled collagen IV specific antibody, whereby if the  
cell does not become labeled with the antibody the cell is identified as a stem cell.

33. A method of inducing a nestin-positive pancreatic stem cell to differentiate into  
20 hepatocytes, comprising the step of:

treating the nestin-positive pancreatic stem cell with an effective amount of an  
agent that induces the stem cell to differentiate into hepatocytes or into progenitor  
cells that differentiate into hepatocytes.

- 25 34. The method of claim 33, wherein the agent is cyclopamine.

35. A method of treating a patient with liver disease, comprising the steps of:  
(a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a

donor; and

(b) transferring the stem cell into the patient, wherein the stem cell differentiates into a hepatocyte.

5     36. The method of claim 35, wherein the patient serves as the donor for said stem cells of step a.

37. A method of treating a patient with liver disease, comprising the steps of:

10     (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) expanding the stem cell *ex vivo* to produce a progenitor cell; and

(c) transferring the progenitor cell into the patient, wherein the progenitor cell differentiates into a hepatocyte.

15     38. The method of claim 37, wherein the patient serves as the donor for said stem cells of step a.

39. A method of treating a patient with liver disease, comprising the steps of:

20     (a) isolating a nestin-positive pancreatic stem cell from a pancreatic islet of a donor;

(b) differentiating the stem cell *ex vivo* to produce a hepatocyte; and

(c) transferring the hepatocyte into the patient.

25     40. The method of claim 39, wherein the patient serves as the donor for said stem cells of step a.

41. A pharmaceutical composition comprising the isolated stem cell of claim 24 admixed with a physiologically compatible carrier.